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Follow-Up in Carriers of the 'MELAS' Mutation without Strokes

Maxwell Simon Damian[a]
Andreas Hertel[d]
Peter Seibel[e]
Heinz Reichmann[e]
Georg Bachmann[b]
Walter Schachenmayr[c]
Gustav Hoer[d]
Wolfgang Dorndorf[a]

Departments of
[a] Neurology and
[b] Radiology, and
[c] Institute of Neuropathology,
University of Giessen,
[d] Department of Nuclear Medicine,
University of Frankfurt, and
[e] Department of Neurology,
University of Dresden, Germany

Abstract

Eight carriers of the A3243G mutation of mitochondrial DNA without stroke-like episodes were monitored for up to 7 years in clinical and metabolic studies, by magnetic resonance imaging (MRI) and positron emission tomography (PET). None developed mitochondrial encephalopathy (MELAS), but 2 developed diabetes mellitus, 1 terminal kidney failure and 2 cardiomyopathy. One patient improved markedly under ubiquinone. Electroencephalography showed progressive slowing in 2 cases, but electrophysiological tests and MRI were otherwise noncontributary. PET showed widespread cortical and basal ganglion metabolic deficits in 6 cases. We conclude that internal medical complications are more common than MELAS in adult carriers of the mutation. PET findings, firstly reported in such patients, suggest that chronic subclinical encephalopathy is very frequent, and PET may play a role in monitoring in the future.

Key Words

Magnetic resonance imaging
MELAS
Mitochondrial disease
Positron emission tomography

Introduction

An A-G transition mutation at nucleotide position 3243 of mitochondrial DNA (mtDNA) is the most common cause of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) [1, 2]. Recent studies have shown that chronic progressive external ophthalmoplegia, diabetes mellitus and renal disease can be caused by the same mutation, and that many carriers of the mutation have only minor symptoms [3, 4]. It remains unknown to what extent oligosymptomatic patients will develop MELAS or any other serious disorder, how closely or by what method carriers of the mutation at nucleotide position 3243 should be monitored, and when they should be treated with enzyme substitution such as ubiquinone. We addressed this problem by following 8 carriers of the mutation without strokes closely for 2–6 years to identify the best monitoring protocol.

Patients and Methods

In this study all patients called our attention after maternal relatives developed MELAS due to a point mutation at nucleotide position 3243 of mtDNA. Patients 1–6 are members of a pedigree carrying the mtDNA 3243 mutation described elsewhere [3]. Their clinical features are summarized in table 1. Patient 8, who was unrelated to the others, developed chronic progressive external ophthalmoplegia and myopathy at age 38 (table 1).

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Dr. M.S. Damian
Neurologische Universitätsklinik
Fetscherstrasse 74
D–01307 Dresden (Germany)
Tel. +49 351 458 2060, Fax +49 351 458 4365

Table 1. Clinical findings

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age at diagnosis	18	15	38	26	32	21	29	41
Sex	female	male	male	male	male	male	female	female
Year of diagnosis	1989	1989	1993	1993	1993	1993	1994	1992
Previous symptoms	short stature acute remitting deafness	short stature	none	exercise intolerance	hyperuricemia	hearing loss hypoglycemic episodes	hearing loss	myopathy hearing loss
Findings at diagnosis	mild proteinuria lactic acidosis mild deafness	mild deafness lactic acidosis proteinuria	mild deafness retinopathy	lactic acidosis	discrete hearing loss hyperuricemia	moderate deafness	mild deafness proteinuria	CPEO, mild tetraparesis mild deafness lactic acidemia
Treatment	ubiquinone since 1991	ubiquinone since 1991	ubiquinone since 1993	ubiquinone since 1993	ubiquinone since 1993	none	none	ubiquinone since 1992
Course	severe deafness 1990 IDDM 1993 episodic abdominal pain	renal failure since 1993 progressive deafness	unchanged	improvement of exercise intolerance	unchanged	acute hearing loss 1993	unchanged	improvement of exercise intolerance
Findings at follow-up	IDDM deafness cardiomyopathy nephropathy	mild deafness renal failure cardiomyopathy	unchanged	unchanged	unchanged	deafness NIDDM	unchanged	tetraparesis improved, otherwise unchanged

IDDM = Insulin-dependent diabetes mellitus; NIDDM = non-insulin-dependent diabetes mellitus; CPEO = chronic progressive external ophthalmoplegia.

The study protocol included a physical examination, blood biochemistry, urinalysis, bicycle exertion tests, glucose tolerance testing, audiometric, ophthalmologic and cardiological examinations. An electroencephalogramm (EEG), visual evoked potentials, brainstem acoustic evoked potentials, somatosensory and motor evoked potentials were performed according to standard procedures. Magnetic resonance imaging (MRI) was done on a 1.5-tesla Siemens Magnetom using T_1 (TR 600 ms/TE 15 ms) and T_2-weighted (TR 3,460 ms/TE 120 ms) spin echo sequences with axial and sagittal 4-mm slices. Complete follow-up was every 2 years, and physical examinations, blood tests and EEG were performed every 6 months. Positron emission tomography (PET) was done on a Siemens ECAT Exact 47 scanner (FOV 16.2 cm) in a dimly lit, quiet room after 12 h fasting. After 30 min of rest, a rapid bolus of ^{18}F-fluorodeoxyglucose (mean 4.7 ± 2.11 MBq per kg body weight) was injected. Dynamic scanning started immediately with 10 scans of 30 s, 3 scans of 300 s and 7 scans of 600 s, in all 90 min. Images were reconstructed by filtered back-projection using a Hann filter (cutoff frequency 0.45 mm × 10^1). Attenuation correction was calculated before using an automatic software procedure (CTI, Knoxville, Tenn., USA). Quantitative metabolic rates of glucose (CMRglc) were calculated using the Patlak graphical method [5], and the metabolic rates (CMRglc) of eight regions of interest of 1-cm thickness calculated according to the template published by Herholz [6]. The regions of interest represented prefrontal, temporal, temporoparietal, parietal, sensorimotor and visual cortex, basal ganglia and cerebellum on each side. A variation of >10% in CMRglc from one cortical area to another or a decrease of >10% in global cortical CMRglc in one area was considered pathological.

Muscle biopsies were obtained from the left biceps brachii muscle in all cases. Frozen sections were stained with hematoxylin and eosin, modified trichrome, periodic acid-Schiff, NADH and succinate dehydrogenase phosphorylase, ATPase (pH 9.4) and oil-red for light microscopy. Electron microscopy was performed from glutaraldehyde-fixed material stained with osmium tetroxide. Biochemical studies of respiratory chain activity were performed from homogenized muscle as described previously [7]. Genomic DNA was isolated from lymphoblasts and from 50 µg of frozen muscle tissue for molecular analysis as reported [3, 8]. The percentage of mutant mtDNA was estimated by quantitative RFLP analysis according to Seibel et al. [9]. DNA was amplified and the PCR reaction mixture supplemented with ^{32}P-labeled dATP after 29 cycles. An additional amplification cycle was carried out. Quantitative Apa I-RFLP analysis was performed and radioactively labeled products were quantitated by scintillation counting.

Results

Table 2 shows paraclinical data and imaging results. Bioptic, biochemical and molecular results are shown in table 3. None of the patients developed stroke-like epi-

Table 2. Paraclinical findings

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Electrophysiology								
At diagnosis	AEP: deformed waves I and II others normal	normal	normal	normal	EEG: mild generalized slowing others normal	normal	normal	EEG: mild generalized slowing
During follow-up	EEG: mild slowing	EEG: mild generalized slowing	normal	normal	unchanged	normal	normal	unchanged
MRI								
At diagnosis	cerebellar hypoplasia	normal	not done (claustrophobia) CT: normal	normal	normal	normal	cerebellar atrophy	normal
During follow-up	unchanged (1994)	normal (1994)		normal	punctate periventricular hyperintensity	normal	unchanged	normal
PET: regional glucose metabolic deficits	cerebellar deficit otherwise normal	basal ganglia right temporal and visual cortex deficits	parietal defect (minimal)	basal ganglia and visual cortex deficits	motor and parietal cortex hypometabolism	markedly reduced unhomogeneous parietal, motor, and right temporal cortex	motor, parietal and temporal cortex deficits	mild parieto-occipital cortex, basal ganglia and cerebellar hypometabolism

AEP = Auditory evoked potential.

Table 3. Bioptic and molecular findings

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Normal values
Muscle biopsy									
LM	mild lipid storage	normal	mild lipid storage	moderate lipid storage	normal	normal	normal	RRF	
EM	deformed mitochondria increased in lateral sarcoplasm	rarely deformed mitochondria, increased mitochondria in lateral sarcoplasm	normal	mild increase in lipid	normal	normal	moderate increase in mitochondria	massive, deformed mitochondria paracristalline inclusions	
Respiratory chain activities, U/g muscle									
ND	54	78	37.5/4.6*	34.6/8.2*	20.2/2.6*	33.5/4.2*	65.4/0.4*	32.4	48 ± 9.4
NC	7.3	12	2.0/1.3*	2.6/1.4*	1.2/0.8*	2.6/1.8*	4.8/3.4*	6.5	3.2 ± 1.5
SD	2.6	3.6	2.2	1.6	1.7	2.6	1.0	2.05	2.4 ± 1.1
SC	3.3	4.5	1.4	1.9	0.9	2.2	1.4	1.5	1.6 ± 0.6
COX	2.3	3.4	2.5	2.9	1.4	3.7	4.7	5.1	2.8 ± 1.0
Citrate synthetase	7.8	9.7							5.3
Molecular analysis									
Percent mutant mtDNA in blood	49	60	17	23	10	15	17	14	
Percent mutant mtDNA in muscle	83	72	42	63	31	23	positive (not quantified)	77	

RRF = Ragged-red fibers; LM = light microscopy; EM = electron microscopy; ND = NADH dehydrogenase; NC = NADH cytochrome c reductase; * = + rotenone; SD = succinate dehydrogenase; SC = succinate/cytochrome c reductase: COX = cytochrome c oxidase.

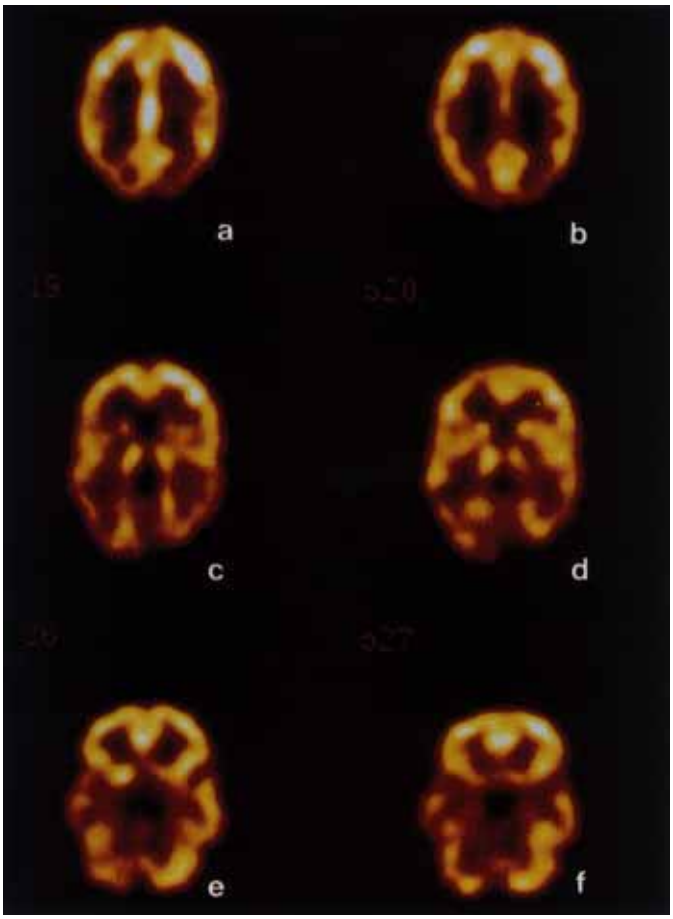

Fig. 1. PET, axial images. Patient 2. a, b Reduced CMRglc in the occipital cortex. c, d Inhomogeneous glucose utilization in the basal ganglia, the caudate nuclei being particularly involved. e, f Reduced right temporal CMRglc.

sodes, but patients 1 and 6 suffered episodes of acute hearing loss, which might possibly represent a 'stroke' of the cochlea. Following treatment with 150 mg ubiquinone/day, exercise tolerance improved in patients 4 and 8, remained unchanged in patients 3 and 5, but patients 1 and 2 developed severe medical complications. Without treatment, patient 6 worsened and patient 7 was unchanged. MRI findings changed minimally only in patient 5. The most common finding on PET was an asymmetrical bilateral reduction in parietal cortical CMRglc (patients 2, 3, and 5–7, fig. 1). Patient 6 had the most marked abnormalities of CMRglc.

Respiratory chain studies revealed increased mitochondrial volume in patients 1 and 2 without a specific defect, and mild carnitine deficiency in patient 1. Patient 7 had low normal complex II activity, but normal succinate dehydrogenase stain light microscopically. The others had low NADH dehydrogenase activity, compatible with a complex I defect; patient 5 also had low succinate-cytochrome c reductase activity, suggesting an additional complex III defect. Patients 1 and 2 had the highest percentages of mutant mtDNA, patients 4 and 8 showed marked heteroplasmy comparing blood and muscle, and the others had generally low (<50%) percentages of mutant mtDNA.

Discussion

MELAS is generally an early-onset syndrome that rapidly causes severe neurological deficits and typically stroke-like episodes associated with an A-G point mutation of mtDNA at nucleotide position 3243. Recently, internal medical conditions, such as diabetes mellitus, cardiomyopathy or kidney failure, have gained attention, either complicating MELAS or on their own [3, 4, 10, 11] in association with the A3243G mutation, which may be an important cause of diabetes mellitus in some populations [12–14]. However, a growing number of asymptomatic or only mildly affected gene carriers have been recognized, and it is at present impossible to determine which carriers will progress to the full-blown syndrome. Clinicogenetic correlations are difficult due to heteroplasmy and because the precise mechanism of the disease caused by the rRNA $Leu^{(UUR)}$ point mutation remains unclear. Asymptomatic patients generally have lower percentages of mutant mtDNA in blood than classical MELAS cases, but this is not a close correlation [3, 4, 15]. The optimal management of presymptomatic carriers has not been defined, because the efficacy of any treatment is unproved [16]. Until now there are few PET studies in mitochondrial encephalopathies [17–20]. Frackowiak et al. [17] showed uncoupling of cerebral oxygen ($CMRO_2$) and CMRglc with preferential depression of the cerebral metabolic rate of oxygen in 4 patients with mitochondrial encephalopathy and complex I deficiency, but without MELAS. Duncan et al. [20] recently demonstrated accelerated CMRglc in 1 child with complex I and 1 with complex IV deficiency. Both had increased cerebral lactate on MR spectroscopy. Yokoi et al. [19] showed decreased aerobic pyruvate turnover, reduced cerebral blood flow and $CMRO_2$ in 6 patients with mitochondrial encephalomyopathies (2 complex III, 3 complex IV deficiencies, no stroke-like episodes). The data are difficult to compare, as the patients were examined at different stages of their disease, had varying defects in the respiratory chain, and

mtDNA mutations were mostly not defined. Interestingly, Castillo et al. [21] reported no basal ganglia involvement in 8 MELAS patients using MR spectroscopy, contrary to our PET findings.

None of our patients showed clinical signs of cerebral involvement at diagnosis. Electrophysiological studies were of limited value for follow-up, only revealing mild generalized EEG slowing in patients 5 and 8, and deformed brainstem acoustic evoked potentials in patient 1. MRI did not show major pathology in our patients without cerebral symptoms. Muscle biopsy showed ragged-red fibers only in patient 8, but mild-to-moderate lipid storage more frequently (patients 1, 3 and 4). Respiratory chain studies most often detected complex I defects. Patients 4 and 8 had >50% mutant mtDNA in muscle despite low percentages in blood and were the only ones with myopathy. However, patients 1 and 2 had even more mutant mtDNA in both muscle and blood, but no muscular symptoms; their follow-up revealed a more severe oxidative disorder than in the other patients, as they were the only ones to develop serious internal medical disorders. Probably patients with >50% mutant mtDNA in several different tissues are at a higher risk of serious disease at an earlier age [3, 15], so a muscle biopsy can help estimate prognosis. The effect of treatment remains unproven; patients with or without treatment remained unchanged, or progressed. Myopathy seemed to be improved by ubiquinone. Our study shows that routine follow-up must include blood tests, EKG and EEG, but other electrophysiological studies and MRI are probably of little value without specific symptoms.

PET revealed widespread abnormalities in 6 patients, with a pattern differing from vascular disorder and from neurodegenerative disorders such as Alzheimer's or Parkinson's disease [6, 22]. CMRglc defects were often patchy or asymmetrical, and involved cortex and deep gray matter. The parietal cortex was most often involved, the basal ganglia next. The prefrontal cortex was never involved. Normal absolute values of CMRglc are still a matter of debate, and for ethical reasons we did not examine a normal control group. However, other workers have demonstrated that under normal conditions intraindividual variations of CMRglc in cortex are very small [23, 24], so we feel that that our observed inhomogeneous CMRglc in gray matter (>10% variation) are truly pathological. Our findings were too heterogeneous to suggest a systematic predilection for a particular area of the brain, contrary to stroke-like lesions, which are very often occipital [25, 26]. The visual cortex was not very frequently involved in our series, which raises the question whether such PET abnormalities are related to stroke-like episodes at all. The pathogenetic mechanisms of cerebral metabolic abnormalities cannot be adequately studied without measurement of oxygen consumption, which revealed uncoupling of glucose metabolism with reduced oxygen consumption per molecule of glucose in the study by Frackowiak et al. [17]. Further study is therefore needed to determine the significance of pathological CMRglc. An interesting parallel might be drawn between reduced CMRglc in the basal ganglia and the cerebral pathology of 2 other members of the family who were autopsied [27]. Their basal ganglia, especially the globus pallidus, showed disseminated microcalcification at an early age (fig. 2) which was not seen

Fig. 2. HE-stained light-microscopic autopsy section of the globus pallidus in a 10-year-old MELAS patient, a sister of patients 1 and 2. Disseminated microcalcification (arrows), possibly correlating to basal ganglion hypermetabolism on PET.

elsewhere in the brain and suggests a chronic degenerative process which could be related to hypometabolism on PET. Thus even in oligosymptomatic patients with normal MRI, cerebral metabolism is markedly abnormal. Long-term follow-up is needed to define the prognostic value of PET. Such patients should be considered at risk of developing acute symptoms, especially in situations that raise the cerebral metabolic demand, such as seizures, or reduce the supply of substrate. MR spectroscopy can directly show regional mitochondrial metabolism, expressed in lactate levels [20, 28]. This cannot be done by PET, which studies mainly extramitochondrial glucose metabolism; on the other hand, the precise clinical relevance of increased lactate is unknown, and PET might help provide a rationale for treatment without waiting for strokes. PET may also play a role in assessing treatment regimens in future studies.

In conclusion, our follow-up study of carriers of the A-G transition at nucleotide position 3243 of mtDNA without stroke-like episodes showed that patients with the mutation can remain neurologically stable over long periods, but frequently develop serious internal medical disorders. This underlines the importance of an early detection of carriers of the mutation by an adequate follow-up including a neurological, general medical and audiometric examination, blood chemistry, urinalysis, EKG and EEG. A high percentage of mutant mtDNA in several tissues may be associated with an unfavorable prognosis, but in many patients PET reveals abnormalities, most often involving the basal ganglia and parietal cortex, before structural damage occurs.

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